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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,647	FIRESTEIN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-37 and 39-54* is/are pending in the application.

4a) Of the above claim(s) *40,42,44,45,48,49 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-39,41,43,46,47 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 10/19/07 in response to the notice of non-compliant amendment has been entered. Claims 1-31 and 38 are canceled and new claims 46-54 have been entered. Claims 32-37, and 39-54 are currently pending in the instant application.

As noted in the previous office action, the applicant has elected without traverse the invention of the composition of claims 32-43, which is drawn to a nucleic acid with a sequence encoding a polypeptide that promotes apoptosis in mammalian cells, and the species a) a nucleic acid encoding p53. New claims 48-49 and 54 are not drawn to the elected subject matter. New claims 48-49 are drawn to a composition comprising a plurality of nucleic acid vectors for expressing a polypeptide that promotes apoptosis and a plurality of fibroblast-like synoviocytes, or a fibroblast-like synoviocyte host cell transfected with a nucleic acid encoding a polypeptide that promotes apoptosis. While the nucleic acid encoding a polypeptide that promotes apoptosis may be present in the newly claimed compositions, the presence of the fibroblast-like synoviocytes renders the newly claimed compositions materially different in structure, physical and chemical properties, and in function. Further, the search and examination of all these compositions together would place a serious and undue burden on the examiner because (a) the inventions have acquired a separate status in the art in view of their different classification; (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter; (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries); (d) the prior

art applicable to one invention would not likely be applicable to another invention; and (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. It is further noted that the applicant has already received a first action on the merits for the elected invention. As such, new claims 48-49 and 54 are withdrawn from prosecution.

This application contains claims 40, 42, 44-45, 48-49 and 54 which have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/19/06. In response to applicant's comment in the instant response that claim 40 should be examined since a p53 polypeptide and a p53 peptidomimetic or binding agent can be searched together without undue burden on the examiner, it is first noted that the applicant has already elected the species of a nucleic acid encoding p53 polypeptide without traverse in the reply filed on 12/19/06. Further, a p53 polypeptide, a p53 peptidomimetic, and a p53 binding agent are all materially different molecules with different physical, chemical, and functional properties such that search for the p53 polypeptide itself will not necessarily reveal any prior art related to p53 peptidomimetics or binding agents. In addition, examination of each of these molecules would be likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. Thus, claim 40 remains withdrawn from prosecution. Claims 32-39, 41, 43, 46-47, and 50-53 are currently under consideration. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Drawings

Applicant's submission of a replacement sheet for a new corrected drawing for Figures 1 and 2 is acknowledged. The replacement Figures are in compliance with 37 CFR 1.121(d).

Priority

The applicant has amended the specification to update the status of parent application 09/363,997. Priority under 35 U.S.C. 120 to 09/363,997 is acknowledged.

Information Disclosure Statement

The information disclosure statement filed 6/27/07 complies with 37 CFR 1.98 and 1.97 and has been considered by the examiner. An initialed and signed copy of the 1449 is attached to this action.

Claim Rejections - 35 USC § 102

The rejection of previously pending claims 32-39, 41, and 43 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 5,747,469 (1998), hereafter referred to as Roth et al., is maintained over amended and new claims 32-37, 39, 41, 43, 46-47, 50-51, and 53, claim 38 having been canceled. Applicant's amendments to the claims and arguments have been fully

considered but have not been found persuasive in overcoming the grounds of rejection for reasons of record as discussed in detail below.

The applicant has amended the claims to recite a composition comprising a therapeutically effective amount of a nucleic acid molecule with a sequence encoding a polypeptide that promotes apoptosis, wherein the composition is formulated for administration into an arthritic or inflamed joint in a mammalian subject and for transfection of synoviocytes, and wherein said amount is effective in reducing signs of arthritis or inflammation upon administration into a joint.

The applicant argues that the claim amendments now patentably distinguish their composition from the compositions taught by Roth. In particular, the applicant argues that the claims now recite that the nucleic acid is "formulated for administration to an arthritic joint and for transfection of synoviocytes". In response, it is first noted that the applicant points to paragraph 59 for support for these new limitations, citing the Patent application publication. However, paragraph 59 states:

> The preferred method of gene therapy is direct gene transfer, i.e., local application of the preparation containing the apoptotic polypeptide-encoding DNA into an afflicted joint or other region of cellular accumulation. In the case of rheumatoid arthritis, this allows targeting to the cells of the synovial intimal lining (e.g., the macrophage and fibroblast-like cells). A variety of well known vectors can be used to deliver the apoptosis-regulating gene to cells in a closed compartment like a joint, including but not limited to adenoviral vectors and adeno-associated vectors. In addition, naked DNA, liposome delivery methods, or other novel vectors developed to deliver the gene to cells can also be beneficial. (paragraph 59 of U.S. Patent Application Publication 2004/00116372).

Thus, the added limitation concerning formulating the nucleic acid for administration to an arthritic joint and for transfection of synoviocytes places no particular limitations on the

claimed composition other than that a well known vector such as an adenoviral vector, adeno-associated vector, naked DNA or liposome delivery method should be used. Roth et al. teaches to formulate a nucleic acid encoding p53 in just such well known vectors including adenoviral vectors, adeno-associated vectors, and DNA in liposomes (Roth et al., column 5). Thus, applicant's argument regarding the "formulation" of the composition is not persuasive.

The applicant further argues that Roth et al. does not teach a "therapeutically effective amount" of a nucleic acid encoding p53, where the amount is "effective in reducing signs or arthritis or inflammation". It is noted that the applicant points to paragraph 74 of the Patent application publication for support for this new limitation. Paragraph 74 discloses the definition of "therapeutically effective amount" as follows:

> "Therapeutically effective" as used herein, refers to that amount of composition that is of sufficient quantity to ameliorate the cause of the cellular accumulation disorder. (paragraph 74 of U.S. Patent Application Publication 2004/00116372).

However, neither this paragraph, nor any other section of the instant specification provides any specific guidance as to what amount of any particular nucleic acid encoding p53 qualifies as "therapeutically effective". The specification does not exemplify any vector encoding p53 nor give any guidance as to particular "amounts" such as pfus of virus or grams of DNA. The specification, as in paragraph 59 cited above, simply teaches to use well known vectors and cites a number of references available in the prior art for their use. Roth et al., on the other hand, provides some specific guidance for therapeutically effective amounts of nucleic acid encoding p53, including 5X10-7 pfu of adenoviral-53 for a mouse and from 1X10-10 to 5X10-12 of adenoviral-p53 for a human (Roth et al., columns 27 and 30). Thus, in the absence of evidence

to the contrary, Roth et al. appears to teach a "therapeutically effective amount" of a p53 nucleic acid. Thus, applicant's arguments regarding a "therapeutically effective amount" is not persuasive.

The applicant then argues that Roth et al. compositions cannot be said to "inherently" possess all of the claimed properties of the instant compositions because Roth et al. teaches the effectiveness of vectors encoding p53 in killing tumor cells and does not teach the effectiveness of vectors encoding p53 in killing synoviocytes in an arthritic joint. In support of their argument, the applicant cites Clayman et al., which includes Roth as an author, for teaching that p53 constructs would not be expected to work in treating arthritis. However, the cited passage from Clayman et al. does not support applicant's arguments. Clayman et al. looked at the effects of Ad5CMV-p53 on "karyotypically normal and nontumorigenic fibroblast cell lines". The fact that Ad5CMV-p53 did not kill these cells is not surprising as these cells already express wild type p53 and are normal. The point of the Clayman et al. article was that the Ad5MCV-p53 can successfully transduce fibroblasts and that while the vector successfully kills tumor cells that lack or have mutated p53, the vectors do not kill normal fibroblasts. These results in no way cast doubt on the inherent ability of the Roth vectors to kill arthritic synoviocytes since arthritic synoviocytes are not considered normal fibroblasts and further comprise mutated p53. Thus, the evidence of Clayman et al. is not found persuasive in overcoming the rejection of record.

In conclusion, Roth et al. appears to teach the exact same nucleic acid compositions as instantly claimed. The structure of the vectors taught by Roth et al. are identical to those disclosed by applicant and claimed in the instant claims. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are

presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Applicant's amendments to the claims has necessitated the following new grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 52 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 52 depends on new claim 47. New claim 47 recites a composition comprising an adeno-associated virus (AAV) vector. New claim 52 adds the limitation wherein "said vector is present in microspheres, liposomes, or macromolecular complexes". The applicant points to paragraph 65 of the Patent application publication for support for this new limitation. However, while paragraph 65 refers to colloidal dispersion systems including microspheres, liposomes and macromolecule complexes, the preceding paragraph, paragraph 64 clearly indicates that the specification envisions the use of these colloidal dispersion systems with non-viral vectors. Neither the indicated paragraph, nor any other portion of the instant specification teaches a composition comprising recombinant AAV vectors present in microspheres, liposomes, or macromolecular complexes. As such, the limitation of new claim 52 represents new matter not supported by the as filed specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50 and 51 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New claims 50 and 51 depend on new claim 47, which depends on claim 35, which depends on claim 32. Claim 50 lack antecedent basis for "said fibroblast-like synoviocytes", as none of claims 32, 35, or 47 recites this limitation.

Claim 51 conflicts with claim 47. Claim 47 already places a limit on the viral vector to an AAV vector. Claim 51 improperly broadens the vector to either an adenovirus or AAV vector. As such, the metes and bounds of the claim cannot be determined.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology

center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633